

# Development and Clinical Evaluation of Intranasal Scopolamine Gel Formulation



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The goal of this research is to develop a noninvasive, efficacious dosage form of scopolamine, the clear drug of choice for the treatment of space motion sickness (SMS). An alternative route of administration – intranasal to oral – aims at circumventing the gastrointestinal dysfunction caused by SMS, thereby enhancing the efficacy. Earlier reports indicate that intranasal dosing with scopolamine increases the absorption rate and bioavailability compared to an equivalent oral dose. Another advantage of intranasal administration of medications is the avoidance of first-pass metabolism by the liver to which certain drugs are subjected after oral administration. This new formulation design is based on the hypothesis that gel formulations are more suited than liquid dosage forms for prophylaxis and treatment of SMS.

Three FDA [Food and Drug Administration]-sponsored clinical trials were designed to characterize pharmacokinetics (PK) and pharmacodynamics, and to evaluate the safety and efficacy of intranasal scopolamine (INSCOP). The first of three trials of the relative bioavailability and PK of INSCOP, conducted at MDS Pharma Services, King of Prussia, Pa., entailed the administration of three doses of INSCOP to 12 subjects to establish the dose range for treatment. In figure 1, the area under the curve, a measure of bioavailability, increases linearly with dose while all other parameters are consistent for all three doses. These results confirm that the bioavailability and PK of scopolamine are linear at the dose range of this investigation.

The second clinical trial, conducted at the Dartmouth-Hitchcock Medical Center (DMC) in Lebanon, N.H., determined the efficacy of two doses of INSCOP for the treatment of motion-induced sickness that was simulated by an off-axis vertical rotation chair in 18 motion-sickness-susceptible subjects. Results suggest that INSCOP is equally efficacious at both low and high doses (0.2 and 0.4 mg), as indicated by the longer chair ride times of subjects who had been administered INSCOP than the times of those who had been administered a placebo.

The third and final clinical trial, conducted at MDS Pharma Services, examined changes in the bioavailability

and PK of two doses of INSCOP in 12 subjects using a ground-based microgravity analog – an antiorthostatic head-down bedrest (ABR) model. Results indicate that: (1) the relative bioavailability of a higher dose (0.4 mg) and not a lower dose (0.2 mg) of INSCOP increased during ABR compared to that available during ambulation; and (2) gender-specific differences exist in the bioavailability and PK of INSCOP during ABR.

We conducted a follow-on collaborative study, funded by Naval Aerospace Medical Research Laboratory, Pensacola, Fla., to examine the relative efficacy of standard treatment regimes of motion sickness to that of INSCOP. Results from this study agreed with those from DMC and confirmed that a 0.4-mg dose of INSCOP was efficacious in suppressing motion sickness symptoms caused by the motion simulator dome, which is another paradigm for motion-induced sickness. Indeed, INSCOP significantly increased time in the dome in motion-susceptible subjects (figure 1). INSCOP was also used by a small number of crew members as needed for treatment of SMS during space flight. Anecdotal reports from crew members and flight surgeons indicate that the formulation was efficacious for the treatment of SMS. We expect to continue to work with the pharmaceutical industry and academia on these types of studies.

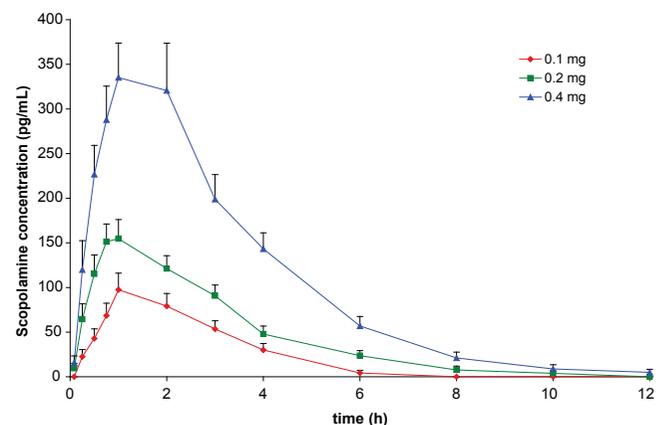


Fig. 1. Plasma concentration-time profiles after INSCOP administration (n=12).